Miliary Mesothelioma

A New Clinical and Radiological Presentation in Mesothelioma Patients with Prolonged Survival After Trimodality Therapy

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Abstract: Malignant pleural mesothelioma is usually a fatal disease and is considered a locally aggressive tumor. Consequently, distant metastases are very rare and a diffuse involvement of the lung is seldom reported. However, due to more efficient chemotherapy protocols and aggressive management strategies including induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation therapy, so called trimodality therapy, survival is prolonged in selected patients. Therefore, new presentations of the disease are appearing with new diagnostic and therapeutic challenges. Herein, we report two cases of treated mesothelioma patients who developed a miliary mesothelioma in the remaining lung 36 and 41 months after undergoing multimodal therapy. Diagnostic assessment and therapeutic strategy are discussed taking into account the different evolutions of each patient.

Key Words: Pleural mesothelioma, Thoracoscopy, Extrapleural pneumonectomy.

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Despite recent therapeutic advances, malignant pleural mesothelioma (MPM) is associated with poor outcome due to the diffuse nature of the tumor with involvement of the surrounding structures and local progression of the disease generally leading to death within 1 year of diagnosis, usually caused by direct extension of the tumor.[1] Typically, distant metastases are clinically not apparent, especially early in the course of the disease, although hematogenous metastases to the contralateral lung, adrenal glands, and liver are found at autopsy in one-third to one-half of patients.[2] Extensive early pulmonary metastases are seldom reported in MPM, and to our knowledge, only three cases have been published in the literature.[3] However, in selected mesothelioma patients undergoing aggressive multimodal therapeutic approach with prolonged survival, recurrences may be characterized by new presentations of the disease, resulting in new diagnostic and therapeutic challenges.

Herein, we report two cases of treated mesothelioma patients who developed a miliary mesothelioma in the remaining lung 36 and 41 months after undergoing multimodal therapy. Diagnostic assessment and therapeutic strategy are discussed taking into account the different evolutions of each patient.

CASE REPORTS

Case 1

A 71-year-old man presented in December 2006 with a 2-week history of left-sided pleuritic lower chest pain, dyspnea on exertion, and cough without sputum. He had a medical history significant for occupational asbestos exposure for 10 years, a 25 pack-year smoking history, and well-controlled hypercholesterolemia. Physical examination revealed a good performance status (PS = 0, ECOG classification), absence of weight loss, and decreased breath sounds at the lower part of the left hemithorax with dullness to percussion. A chest radiograph showed a left-sided pleural effusion confirmed by a computed tomography (CT) of the chest but without pleural nodules, pleural thickening, or parenchymal abnormalities. The pleural cavity was assessed by thoracoscopy showing pleural carcinomatosis suggestive of primary pleural cancer. The histological findings were consistent with the diagnosis of epithelial malignant mesothelioma. The patient was enrolled in the phase II research protocol EORTC 08 031 (European Organization for Research and Treatment of Cancer).[4] According to the protocol, the patient received chemotherapy. After three cycles of chemotherapy combining cisplatinum (75 mg/m^2) and pemetrexed (500 mg/m^2) every 3 weeks, a CT scan evaluation showed stable disease. Ten weeks later, the patient underwent a left-sided extrapleural pneumonectomy (EPP) followed by radiotherapy on the entire hemithorax (54 Gy, 30 fractions). Follow-up was performed at 3-month intervals during the first year and every 6 months thereafter. Thirty-two months after

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completion of the trimodality therapy, the patient reported some weight loss, increasing dyspnea, and right-sided chest pain. Assessment of the chest by CT showed innumerable lung nodules with miliary distribution, pleural effusion, and mediastinal lymphadenopathy (Figure 1). Because of the extensive smoking history and the presentation thought atypical for recurrence of MPM, an endobronchial ultrasound biopsy of the mediastinal lymph nodes was performed (stations 7 and 4R) with an unanimous diagnosis of metastatic epithelial mesothelioma from the French mesothelioma panel of pathologists (MESOPATH) (Figure 2). Despite resuming chemotherapy using the same initial combination and, after the failure of three cycles, the introduction of "second-line" chemotherapy by valproate-doxorubicin combination,[5] the patient died 40 months after the diagnosis.

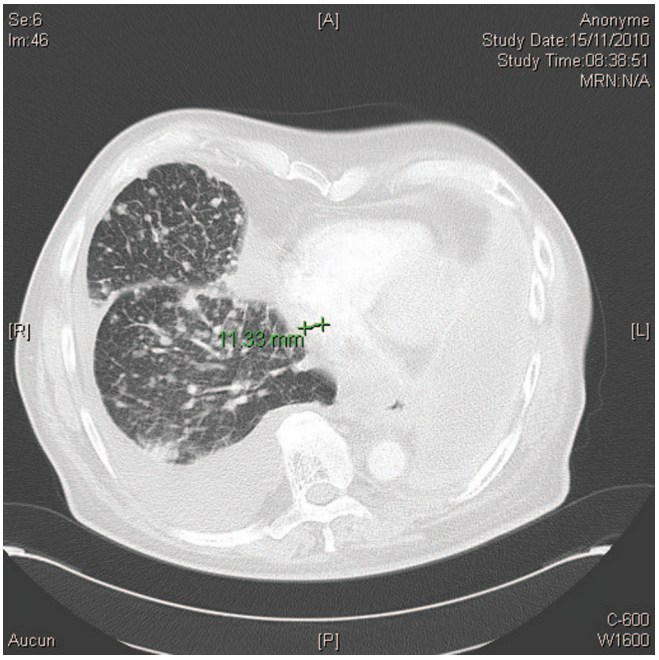

FIGURE 1. Case 1: Computed tomography of the chest showing diffuse parenchymal nodularity on the remaining lung, lymphangitis, and pleural effusion.

Case 2

A 64-year-old man with an occupational asbestos exposure, smoking history (40 pack-years), and an otherwise noncontributory medical history underwent in October 2006 a medical thoracoscopy for the diagnosis of a right-sided pleural effusion leading to the diagnosis of epithelial malignant mesothelioma. After a careful staging and preoperative evaluation, the decision of our multidisciplinary oncologic institutional team was to proceed with trimodality therapy including three cycles of chemotherapy (cisplatinum-pemetrexed) started in November 2006, followed by EPP (February 2007) and ipsilateral radiotherapy (55 Gy/30 fractions) which was completed in May 2007. Clinical and radiological follow-up carried out every 3 months showed no sign of recurrence until November 2010. The patient then presented with severe dyspnea at rest with profound hypoxemia and hypocapnia requiring continuous nasal oxygen supplementation (4 L/min). The physical examination revealed a 5-cm subcutaneous metastatic nodule at the level of a former chest tube insertion site suggestive of mesothelioma recurrence. CT scan of the chest revealed a miliary metastatic pattern in the remaining lung (Figure 3). The therapeutic strategy consisted of chemotherapy using the same cisplatinum-pemetrexed combination with a CT scan evaluation every two cycles. After the first two cycles, the patient dramatically improved with a radiological objective response. After six cycles of chemotherapy, the patient's ECOG performance status was 0, he was clinically asymptomatic, did not require oxygen supplementation, and there was complete resolution of the subcutaneous nodule. Figure 4 shows the last CT scan (May 2011) 3 months after the last cycle of chemotherapy. The patient continues to be followed every 3 months.

DISCUSSION

MPM, unlike lung cancer, is presumed to progress locally by invasion of locoregional organs such as pericardium, ipsilateral lung parenchyma, entire pleural cavity, and

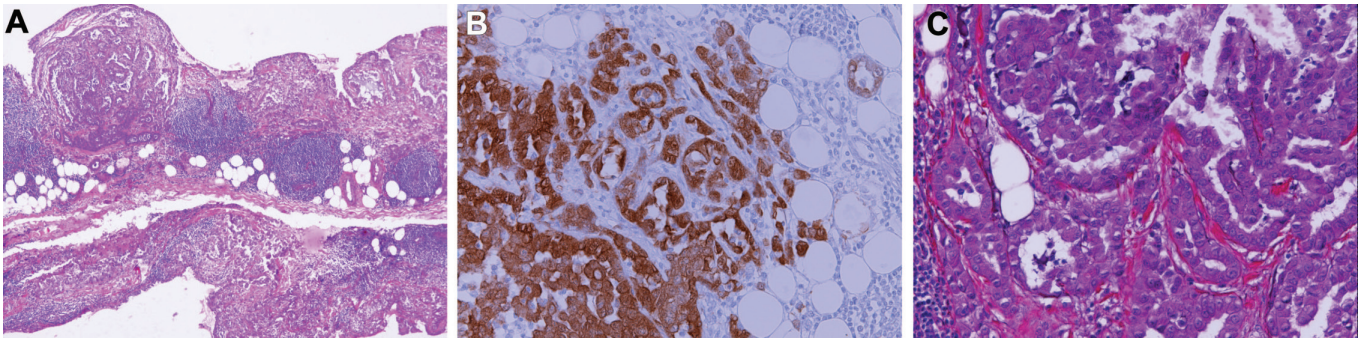

FIGURE 2. Endobronchial ultrasound biopsies at the time of recurrence. *A*, Representative image of diffuse tubulopapillary proliferation of mesothelial origin with invasion of the adipose tissue. *B*, Immunohistochemical staining-diffuse cytoplasmic and nuclear staining with anticalretinin of mesothelial cells. Few cells are observed between adipocytes (magnification ×400). *C*, Tubular architecture. Mesothelial cells are cuboid with central round nuclei without mitosis (hematoxylin & eosin stain, magnification ×400).

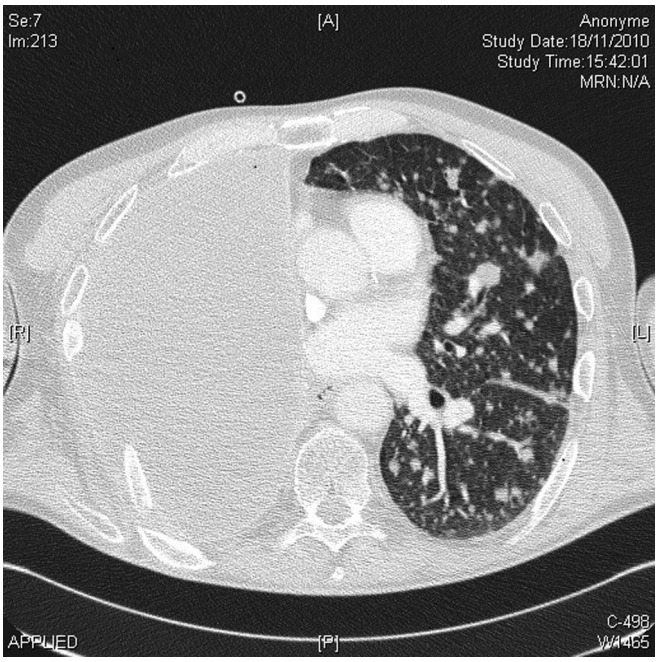

FIGURE 3. Case 2: Computed tomography scan of the chest at admission (November 2010) showing multiple nodules on the left lung.

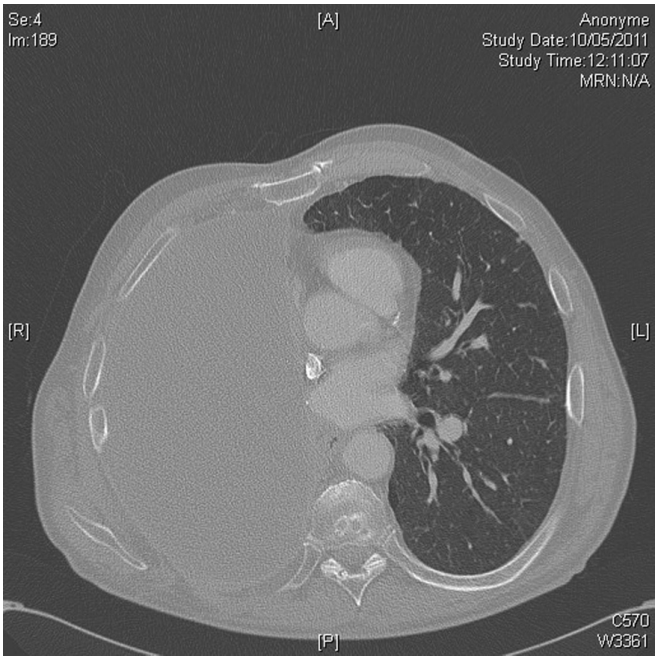

FIGURE 4. Case 2: Computed tomography scan of the chest 3 months (May 10, 2011) after the last cycle of chemotherapy (six cycles). Spectacular improvement of the chest imaging with complete response.

chest wall, ultimately leading to the patient's death. Contralateral lung metastases are rarely identified.[3] The treatment of MPM remains a challenge despite new therapeutic agents showing efficacy leading to longer survival.

Over the past few years, EPP has played an increasingly important role in the management of MPM for selected patient.[6] This surgical procedure, when compared with pleurectomy/decortication, is thought to decrease the local recurrence rate with or without adjuvant hemithoracic radiation.[7,8] However, distant recurrences after a bimodality treatment are frequent as published by several authors.[8] These results provide a rationale for a trimodality therapy combining chemotherapy to EPP and hemithoracic radiation using a combination of cisplatinum with pemetrexed or raltitrexed. Neo- or adjuvant setting of this chemotherapy still remains undetermined due to the lack of randomized studies.[9] However, in selected patients undergoing such trimodality treatment, prolonged survivals are possible, potentially leading to late and atypical recurrences diagnosed during the necessary and continuing follow-up.

In MPM, tumor spread is usually thought to be mainly localized, but the clinical presentation of our two cases argues for the possibility of hematogenous or lymphatic spread as represented by miliary dissemination resulting in respiratory failure. The same mechanism should be invoked for brain, bone, or other distant metastases reported by other investigators.[10,11] The disease progression in the presented cases were different using the same cisplatinum-permetrexed chemotherapy protocol. In case 1, after two cycles of chemotherapy, the disease still remained in progression even with a "second-line" chemotherapy combining doxorubicin and valproate,[5] leading to the patient's death. In case 2, the patient began to improve after the two first cycles of the same protocol with a near-complete response after six cycles and still remained a responder 3 months after the last cycle of chemotherapy. To our knowledge, this is the first report of late miliary mesothelioma in patient undergoing trimodality therapy showing such a spectacular radiological and clinical response after retreatment with pemetrexed-based chemotherapy.

Nowadays, there are no known reported phase III studies defining the role of second-line treatment for MPM. Retreatment with pemetrexed-based chemotherapy has previously shown promising results in the literature. Razak et al. retreated four mesothelioma patients presenting local recurrences (24 months for two patients, 33 months, and 72 months after the end of the initial treatment) using the same pemetrexed-based protocol. Two of them, previously responders to the first-line treatment, achieved a partial response to retreatment, with a time to progression of 5.0 or 8.2 months.[12] More recently, Hayashi et al. reported four cases of patients who had initial durable responses with pemetrexed-based chemotherapy who were retreated with a similar regimen upon progression of their mesothelioma.[13] Further studies are needed to conclude that patients with recurrent epithelioid MPM, initial tumor regression, and a time to progression of 6 months or more after the initial chemotherapy could be good candidates for such management.

Even though recently published guidelines for the management of mesothelioma suggest a more conservative approach confining the indication of EPP to clinical trials,[14] there is no consensus due to the lack of comparative studies. However, the survey carried out among more than 800 surgeons involved in

the care of mesothelioma patients showed that EPP was believed to be more effective than pleurectomy/decortications, and the addition of adjuvant chemotherapy and multimodality therapy were believed to increase the chance of cure.[15] Consequently, physicians should be aware of the possible atypical presentations of recurrent MPM in patients undergoing multimodal approach during the follow-up.

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